This is the accepted manuscript of the article, which has been published in
*Multiple Sclerosis and Related Disorders*. 2020, 38,101498.
https://doi.org/10.1016/j.msard.2019.101498

# Risk factors for reactivation of clinical disease activity in multiple sclerosis after natalizumab cessation

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Highlights of the study

- Clinical relapses were documented in 36 % of patients between 0-12 months
- Corticosteroid-treated relapses occurred in 30 % of patients between 0-12 months
- High disease activity and EDSS ≥ 5.5 before natalizumab predicted reactivation
- Subsequent treatments failed to prevent reactivation
- Washout time > 3 months was associated with an increased reactivation risk

Abstract

Background

Natalizumab (NTZ) is widely used for highly active relapsing-remitting multiple sclerosis (MS). Inflammatory disease activity often returns after NTZ treatment discontinuation. We aimed to identify predictive factors for such reactivation in a real-life setting.

Methods

We conducted a retrospective survey in four Finnish hospitals. A computer-based search was used to identify all patients who had received NTZ for multiple sclerosis. Patients were included if they had received at least six NTZ infusions, had discontinued treatment for at least three months, and follow-up data was available for at least 12 months after discontinuation. Altogether 89 patients were analyzed with Cox regression model to identify risk factors for reactivation, defined as having a corticosteroid-treated relapse.

Results

At 6 and 12 months after discontinuation of NTZ, a relapse was documented in 27.0 % and 35.6 % of patients, whereas corticosteroid-treated relapses were documented in 20.2 % and 30.3 % of patients, respectively. A higher number of relapses during the year prior to the introduction of NTZ was associated with a significantly higher risk for reactivation at 6 months (Hazard Ratio [HR] 1.65, $p<0.001$) and at 12 months (HR 1.53, $p<0.001$). Expanded

Disability Status Scale (EDSS) of 5.5 or higher before NTZ initiation was associated with a higher reactivation risk at 6 months (HR 3.70, p=0.020). Subsequent disease-modifying drugs (DMDs) failed to prevent reactivation of MS in this cohort. However, when subsequent DMDs were used, a washout time longer than 3 months was associated with a higher reactivation risk at 6 months regardless of whether patients were switched to first-line (HR 7.69, p=0.019) or second-line therapies (HR 3.94, p=0.035). Gender, age, time since diagnosis, and the number of NTZ infusions were not associated with an increased risk for reactivation.

Conclusion

High disease activity and a high level of disability prior to NTZ treatment seem to predict disease reactivation after treatment cessation. When switching to subsequent DMDs, the washout time should not exceed 3 months. However, subsequent DMDs failed to prevent the reactivation of MS in this cohort.

Keywords

Multiple sclerosis; natalizumab; discontinuation; reactivation; rebound

NTZ = natalizumab, MS = multiple sclerosis, HR = hazard ratio, EDSS = Expanded Disability Status Scale, DMD = disease-modifying drug, RRMS = relapsing-remitting multiple sclerosis, VCAM-1 = vascular-cell adhesion molecule 1, CNS = central nervous system, PML = progressive multifocal leukoencephalopathy, SPMS = secondary-progressive multiple sclerosis, MRI = magnetic resonance imaging, CI = confidence interval, SD = standard deviation

## 1. Introduction

Natalizumab (NTZ) is a humanized monoclonal antibody used in the treatment of relapsing-remitting multiple sclerosis (RRMS)(Clerico et al., 2017). It is administered intravenously in every four weeks. NTZ has been proven effective in reducing the recurrence of relapses in multiple sclerosis (MS), and it is generally used in patients with a highly active course of disease or a poor response to the first-line therapies of MS(Kappos et al., 2011; Tramacere et al., 2015). By binding to the α4 subunit on α4β1 integrin, NTZ blocks the binding of these integrins to the vascular-cell adhesion molecule 1 (VCAM-1), which is expressed on the endothelial cells of blood vessels in the central nervous system (CNS)(Léger et al., 1997; Yednock et al., 1992). As a result, the migration of T-lymphocytes from the circulation to the CNS is prevented. The therapeutic effect of NTZ is mostly explained by this regulation of T-lymphocyte adhesion and migration across the blood-brain barrier, but other α4-mediated effects of NTZ have also been suggested(Rice et al., 2005).

The use of NTZ is limited due to the risk of progressive multifocal leukoencephalopathy (PML)(Tan and Koralnik, 2010). The risk of PML is increased in patients with long treatment periods, prior immunosuppressive treatment, and positive status with respect to anti-JC virus antibodies(Bloomgren et al., 2012). If the risk is considered too high, switching to an alternative disease-modifying drug (DMD) should be considered.

In Finland, national treatment guidelines are followed when selecting DMDs for MS(Multiple Sclerosis: Current Care Guidelines, 2019). In the Finnish national guidelines, NTZ is positioned either as a first-line or second-line therapy for highly active RRMS with no anti-JC virus antibodies. Cessation of treatment is advised if seroconversion occurs. NTZ is officially licensed only for RRMS in Finland, but it is sometimes used in secondary-

progressive multiple sclerosis (SPMS) patients who experience clinical relapses(Multiple Sclerosis: Current Care Guidelines, 2019).

NTZ is cleared from circulation in approximately two months after discontinuation of treatment, but some residual effects may persist for up to 6 months(O'Connor et al., 2011; Stüve et al., 2006). As expected, reactivation of MS has been shown to occur during the first year after discontinuation of NTZ in some patients(Fox et al., 2014; Gueguen et al., 2014; Havla et al., 2011; Iaffaldano et al., 2015; Kerbrat et al., 2011; Lo Re et al., 2015; O'Connor et al., 2011; Salhofer-Polanyi et al., 2014; West and Cree, 2010). A recent systematic review and meta-analysis of six studies demonstrated that younger age, higher number of relapses and gadolinium-enhancing lesions before initiation of treatment as well as fewer NTZ infusions were associated with an increased risk for disease reactivation after cessation of treatment(Prosperini et al., 2019).

There are no established guidelines on how to treat MS patients discontinuing NTZ therapy, but recent reports have suggested that subsequent treatment with other DMDs should be initiated within 3 months after discontinuation in order to prevent disease reactivation(Iaffaldano et al., 2015; Jokubaitis et al., 2014; Kappos et al., 2015; Lo Re et al., 2015; Salhofer-Polanyi et al., 2014). However, most of the current evidence comes from observatory studies with heterogeneous study settings, and only few randomized trials have been published(Fox et al., 2014; Kappos et al., 2015; O'Connor et al., 2011). Our purpose was to evaluate the predictive factors for post-NTZ disease reactivation in an unselected clinical cohort of MS patients in a real-life setting.

## 2. Material and methods

### 2.1 Study population

This retrospective study was carried out using data from four Finnish hospitals covering a catchment area of 1.3 million residents. Three university hospitals (Kuopio University Hospital, Tampere University Hospital and Oulu University Hospital) from different parts of Finland and one medium-sized central hospital (Central Hospital of Mikkeli) were chosen to represent MS treatment in Finland. The study was approved by the Research Ethics Committee of the Northern Savo Hospital District, Kuopio, Finland, and had an institutional approval from each participating hospital.

MS patients were identified by a computer-based search using the ICD-8, -9 or -10 diagnosis of MS and treatment with NTZ as search criteria. Patients were included in the study if they had received at least six consecutive infusions of NTZ before the treatment was discontinued and follow-up data was available for at least 12 months after the last infusion. A discontinuation was defined as a three-month period without any NTZ infusions. Shorter gaps between infusions were not considered relevant. We identified a total of 101 MS patients who had discontinued NTZ treatment in years 2009-2016, and 89 of them met the inclusion criteria. A flowchart displaying the selection of the study cohort is shown in Figure 1.

### 2.2 Methods

The patient records were systematically reviewed from the time of the first symptom to the latest available contact with the hospital. Data was collected from both paper archives and the hospital districts' electronic patient information systems. The following variables were collected: gender; onset symptom of MS; time from diagnosis to the initiation of NTZ

treatment; existence of gadolinium-enhancing lesions in the pre-NTZ magnetic resonance imaging (MRI) scan; number of NTZ infusions; adverse events during NTZ treatment; primary reason for the discontinuation of NTZ; prior and subsequent DMDs; washout time between DMDs; and all courses of corticosteroid treatment. Age was collected both at the time of diagnosis and at NTZ initiation. Expanded Disability Status Scale (EDSS) was collected at diagnosis, at NTZ initiation, and at NTZ discontinuation. The number of relapses during the year before NTZ initiation and the year after NTZ discontinuation were collected. In our analysis, the onset symptom of MS was also regarded as a relapse. Relapses were collected in two categories. First, all reported relapses were collected regardless of whether they required corticosteroid treatment or not. Second, only relapses which required corticosteroid treatment were collected. The latter were used to define reactivation in the statistical analysis.

Reactivation was defined as having experienced at least one corticosteroid-treated relapse after NTZ discontinuation. Rebound was defined as an increase in the yearly number of all relapses after the discontinuation of NTZ treatment when compared to the year before the initiation of NTZ. Washout time was defined as the time between the last infusion of NTZ and the initiation of the following treatment. In the analysis, EDSS was categorized into two groups with a cut point of 5.5.

### 2.3 Statistical analysis

Univariate Cox regression model was first used to identify individual variables associated with the risk of reactivation at 6 and 12 months of follow-up. Variables with statistically significant associations in the univariate model were then re-analyzed with multivariate Cox regression. The effect of subsequent DMDs administered after the cessation of NTZ

treatment was analyzed using univariate Cox regression with patient as a random effect, and subgroup analysis was performed to determine whether a washout of 0-3 months or longer than 3 months was associated with the risk of reactivation. Results of the Cox regression analyses are shown as hazard ratios (HR) with 95 % confidence intervals (CI). Statistical analysis for the risk of rebound was not performed, as there were only few cases representing possible rebound in the cohort. Data was expressed as means with standard deviations (SD) or frequencies with percentages. Statistical analysis was performed using SPSS Statistics 24.0 and R version 3.5.1. Statistical significance was defined as two-tailed $p < 0.05$.

## 3. Results

### 3.1 Patient characteristics

A total of 89 patients were included in the study. At the time of NTZ initiation, 95.5 % (n=85) had RRMS and 4.5 % (n=4) had SPMS. The patients received a mean number of 26.9 (range 6-85, SD±15.7) infusions of NTZ. Clinical characteristics of the study cohort are shown in Table 1.

Other DMDs were used before NTZ in 85.4 % (n=76) of the patients (Table 2). The most common preceding DMD immediately prior to the initiation of NTZ was glatiramer acetate (39.3 %, n=35). NTZ was used as a first-line therapy in 14.6% (n=13) patients. Of these 13 treatment-naive patients, five had been observed without treatment for more than 12 months after the diagnosis of MS. For the rest of the treatment-naive patients (n=8), NTZ was initiated within 12 months after the first symptom.

In the pre-NTZ MRI scan, 32.6 % of the patients (n=29) in the study cohort had gadolinium-enhancing lesions, while 67.4 % (n=60) had no gadolinium-enhancing lesions.

Altogether 15 patients (16.9 %) had EDSS of 5.5 or higher at the initiation of NTZ treatment, indicating a high level of disability before the initiation of NTZ. All of these patients had RRMS and eight of them had gadolinium-enhancing lesions at the pre-NTZ MRI scan. In 13 of these patients, the primary reason for initiating NTZ was aggressive course of disease, a poor response to earlier DMDs, or both. For the final two patients, the reason for initiating NTZ was marked radiological activity without clinical relapses.

NTZ was mostly well-tolerated. The following adverse events were reported during treatment: fatigue (7.9 %, n=7); skin symptoms (4.5 %, n=4); nausea (3.4 %, n=3); arrhythmia (3.4 %, n= 3); headache (2.2 %, n=2); and fever (1.1 %, n=1). However, only

three patients (3.4 %) discontinued treatment primarily due to adverse events. Skin symptoms reported in the study cohort included two cases of urticaria, one case of unspecified dermatitis, and one case of exacerbation of pre-existing atopic dermatitis. Of these four cases, only the exacerbation of atopic dermatitis led to discontinuation of NTZ treatment. The other two adverse events leading to treatment discontinuation were fatigue and fever. No cases of PML were reported in the study cohort. As expected, positive status with respect to anti-JC virus antibodies was by far the most common reason for discontinuing treatment (57.7 %, n=51). All reasons for treatment discontinuation are shown in Table 1.

After discontinuation of NTZ, subsequent DMDs were initiated for 68.5 % (n=61) and 77.5 % (n=69) of the patients by the time of 6 and 12 months, respectively. Altogether 21.3 % (n=19) of the patients continued without treatment through the first 12 months of follow-up. Table 3 demonstrates the distribution of patients according to the use of subsequent DMDs and the length of washout time. The most common subsequent treatment was fingolimod (52.8 %, n=47). Other subsequent DMDs included subcutaneous interferons (9.0 %, n=8), glatiramer acetate (8.9 %, n=8), dimethyl fumarate (4.5 %, n=4), and alemtuzumab (2.2 %, n=2). In addition to DMDs, nine patients (10.1 %) received preventive high-dose corticosteroids without a clinical relapse within three months after the discontinuation of NTZ. Five of these courses of corticosteroids were given during the first month after discontinuation.

### 3.2 Reactivation of MS after discontinuation of NTZ

During the first 6 and 12 months of follow-up after the discontinuation of NTZ, a relapse was documented in 27.0 % (n=24, Table 1) and 35.6 % (n=32) of the patients, respectively. By the time of 6 and 12 months, 20.2 % (n=18) and 30.3 % (n=27) of patients had experienced a

relapse which required corticosteroid treatment, thus meeting our definition for reactivation. The proportions of patients experiencing corticosteroid-treated relapses according to the use of subsequent DMDs and the length of washout are demonstrated in Table 3.

The results of the Cox regression analyses are shown in Table 4. A higher number of relapses during the year before NTZ initiation was associated with a significantly higher risk for reactivation at 6 months (HR 1.65, 95 % CI 1.26-2.15, $p<0.001$) and 12 months (HR 1.54, 95 % CI 1.21-1.96, $p<0.001$) of follow-up. EDSS of 5.5 or higher at the time of NTZ initiation was associated with a significantly higher risk for reactivation at 6 months (HR 3.70, 95 % CI 1.23-11.15, $p=0.020$) but not at 12 months of follow-up when compared to patients with less disability (EDSS 0-5.0). Conversely, EDSS of 5.5 or higher at the time of NTZ discontinuation was associated with a significantly higher risk for reactivation at 12 months (HR 2.63, 95 % CI 1.12-6.20, $p=0.027$) but not at 6 months of follow-up.

According to the univariate analysis, the following variables were not associated with the risk of clinical reactivation after discontinuation of NTZ: gender; age at the initiation of NTZ treatment; time from diagnosis; number of NTZ infusions; and multifocal onset symptoms when compared to other forms of disease onset. These non-significant variables were not included in the multivariate model.

Univariate Cox regression model with patient as a random effect was used to analyze the effect of subsequent DMDs after NTZ cessation on the risk of reactivation. In this analysis, the patients' status with respect to DMDs was classified into three groups, which were compared with each other: first-line therapies (dimethyl fumarate, glatiramer acetate, and interferons); second-line therapies (alemtuzumab and fingolimod); and no DMDs. Subgroup analysis was done separately to compare patients with a washout time of 0-3 months to patients with a washout time longer than 3 months. According to the analysis, the use of

subsequent DMDs was not significantly associated with the risk of reactivation at 6 or 12 months of follow-up. The results were the same in the first-line and second-line therapy group. However, the subgroup analysis showed that patients switching to subsequent DMDs after a washout longer than 3 months were in fact at higher risk for reactivation (Table 4) when compared to patients without treatment.

Altogether eight patients (9.0 %) showed clinical signs of rebound activity according to the number of relapses they experienced during the year after NTZ discontinuation. These patients experienced their first clinical relapse 1-4 months after discontinuation of NTZ with a median of 3 months. Data of all patients who experienced rebound are shown in Table 5.

## 4. Discussion

In our study, we demonstrated that 20.2 % of patients experienced clinical reactivation of MS within 6 months after discontinuation of NTZ. In previous studies, the proportion of patients experiencing relapses after NTZ discontinuation has ranged from 13.5 to 58 % (Jokubaitis et al., 2014; Sangalli et al., 2014; West and Cree, 2010). This variability reflects differences in study populations and the difficulty of defining what constitutes as a relapse. We avoided this problem by using only corticosteroid-treated relapses to define reactivation.

We demonstrated that a high number of relapses during the year prior to NTZ initiation was significantly associated with an increased risk for reactivation. Our findings are in line with the majority of previous reports.(Jokubaitis et al., 2014; Lo Re et al., 2015; Papeix et al., 2016). However, there is one retrospective study reporting an opposite finding where lower annual relapse rate was associated with an increased risk for reactivation (Salhofer-Polanyi et al., 2014).

We also found that EDSS of 5.5 or higher at the initiation of NTZ was a risk factor for the reactivation of MS at 6 months, and EDSS of 5.5 or higher at the discontinuation of NTZ at 12 months of follow-up. To our knowledge, there are no previous reports on marked disability being a risk factor for reactivation of MS after NTZ cessation. We find this to be of interest, since high EDSS is often associated with SPMS, in which peripheral inflammation has been considered to be minimal. In our cohort, none of the patients with EDSS of 5.5 or higher at the initiation of NTZ were defined as having SPMS. Since this is a retrospective study, it must be taken into consideration that this might be false and the group could represent SPMS patients with activity(Lublin, 2014). The pathogenesis of SPMS is still partially unknown, but it seems that there is compartmentalized smoldering inflammation in the CNS(Correale et al., 2017), which might activate under certain conditions. On the other

hand, the patients in our cohort may have had high EDSS due to residual symptoms from previous severe relapses and therefore they were true RRMS patients despite the high EDSS.

Controversial findings have been reported about the association between the number of NTZ infusions and the risk for reactivation, as some studies have reported higher reactivation rates in patients with shorter exposure to NTZ(Lo Re et al., 2015; Miravalle et al., 2011; Prosperini et al., 2019; Vellinga et al., 2008). In our analysis, we did not detect any correlation between the number of NTZ infusions and the risk for reactivation. Furthermore, there was no correlation between age and reactivation risk, which is in line with a majority of earlier studies(Jokubaitis et al., 2014; Lo Re et al., 2015; Salhofer-Polanyi et al., 2014).

A previous study by Iaffaldano et al has demonstrated the superiority of fingolimod in comparison to interferon beta and glatiramer acetate in controlling post-NTZ disease reactivation.(Iaffaldano et al., 2015). However, in our study none of the treatment strategies used after NTZ were able to significantly control reactivation of MS. Furthermore, previous reports suggest that subsequent DMDs should be initiated as soon as possible after discontinuation of NTZ to prevent reactivation(Iaffaldano et al., 2015; Kappos et al., 2015). In the present study, a short washout time did not reduce reactivation, but a washout time longer than 3 months was significantly associated with an increased risk of reactivation. However, the number of patients switching to subsequent DMDs within 3 months after NTZ was very small in our study, which may explain why the selected treatment strategies did not reduce reactivation risk in the analysis.

Some of the previous studies have also identified a so-called rebound phenomenon or rebound effect after discontinuation of NTZ (Gueguen et al., 2014; Kerbrat et al., 2011; Lo Re et al., 2015; Salhofer-Polanyi et al., 2014; Sangalli et al., 2014; Vellinga et al., 2008). However, literature lacks a precise definition of the rebound effect, and not all studies have

confirmed its existence(O'Connor et al., 2011). We defined rebound as an increase in the number of yearly relapses after discontinuation of NTZ when compared to the year before NTZ initiation and discovered that 9 % of our patients had experienced rebound activity. This is somewhat lower than what has been reported in the majority of earlier reports(Gueguen et al., 2014; Kerbrat et al., 2011; Lo Re et al., 2015), but almost similar to what was reported in two earlier studies(Salhofer-Polanyi et al., 2014; Sangalli et al., 2014).

The study has limitations that should be noted. Due to the retrospective setting, some data were missing. Although it is a common custom in Finland for patients using DMDs to attend regular follow-up visits with neurological examinations, EDSS was not always documented. Furthermore, a substantial part of MRI data was missing. Therefore, we could not use it in the regression analysis. When describing pre-NTZ MRI, we only reported whether gadolinium-enhancing lesions were present, as the exact number of lesions was not reported for every patient.

We find the strength of this study to be its coverage of a large catchment area, the inclusion of four hospitals from different parts of Finland, and the use of an unselected real-life case series. The existence of our national treatment guidelines makes our data uniform and well representative of the actual treatment that Finnish MS patients received in years 2009-2016. Due to our national treatment guidelines, the indications for using different DMDs for reducing disease activity and prescribing corticosteroids for relapses in MS are concordant between different study centers.

Since approximately a fifth of MS patients discontinuing NTZ seem to suffer from reactivation regardless of the duration of their treatment, we suggest that NTZ should only be initiated with the purpose of using the treatment for long periods. None of the therapeutic strategies used in this cohort were able to control the return of disease activity. In the future,

the efficacy of the more recently approved DMDs in preventing post-NTZ disease reactivation should be evaluated. Until then, close attention should be paid on patient selection, regarding fertile women with family plans in particular. Washout times should be kept as short as possible after NTZ cessation.

## 5. Conclusions

Discontinuation of NTZ treatment may lead to a marked reactivation of MS. High disease activity and a high level of disability prior to NTZ initiation seem to predict such reactivation, which could not be prevented with subsequent DMDs. A washout time longer than 3 months was a risk factor for post-NTZ disease reactivation.

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Figure 1. The selection of the study cohort. NTZ = natalizumab.

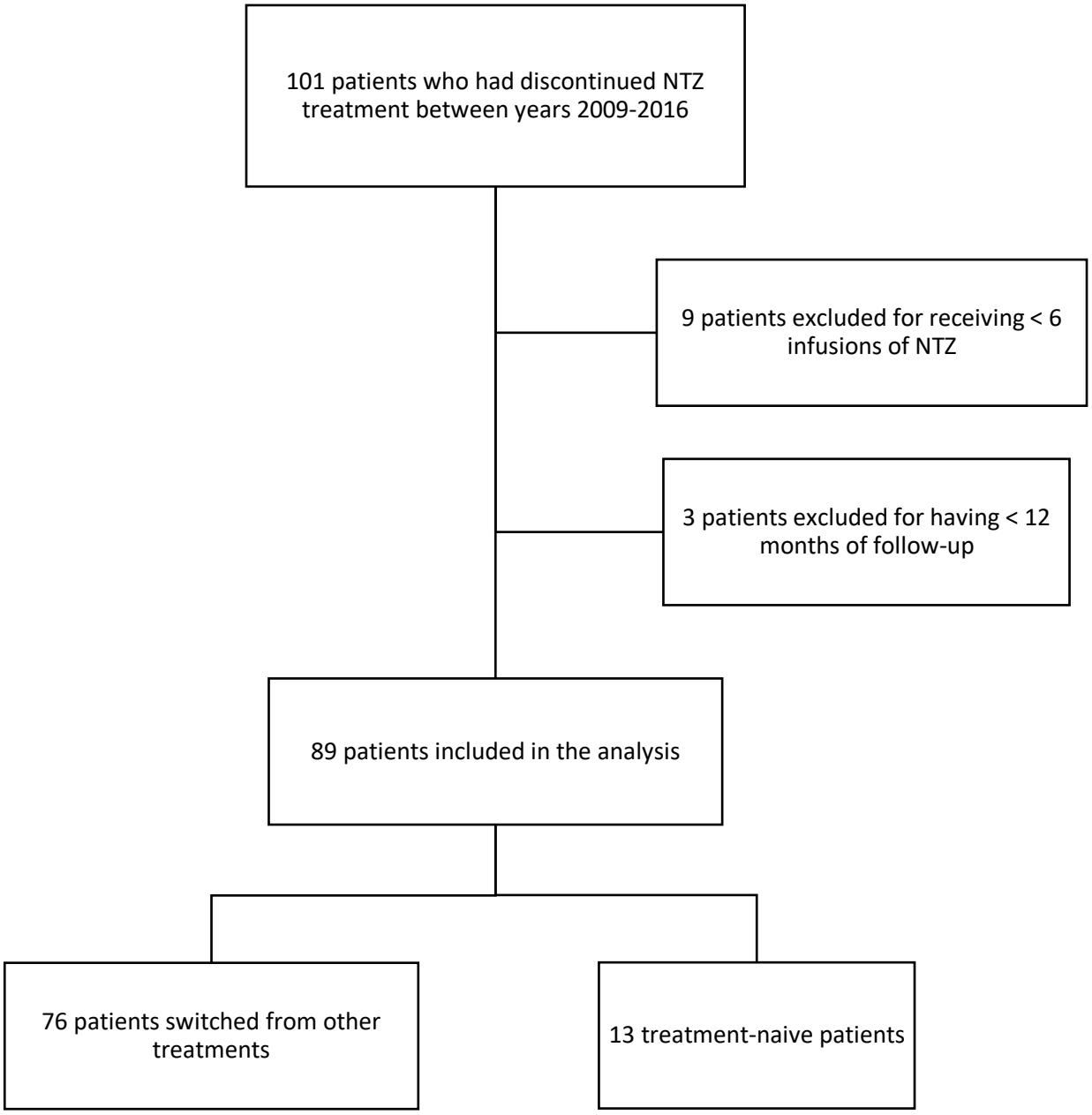

Table 1. Clinical characteristics of the study cohort (n=89). SD = standard deviation, NTZ = natalizumab, EDSS = Expanded Disability Status Scale, PML = progressive multifocal leukoencephalopathy. *Positive anti-JC virus antibodies, long treatment period and/or prior immunosuppressive treatment

| | Patients with at least one relapse at 6 months after cessation (n=24) | Patients with no relapses at 6 months after cessation (n=65) | All patients (n=89) |
|---|---|---|---|
| Female gender, n (%) | 17 (70.8 %) | 46 (70.8 %) | 63 (70.8 %) |
| Age at the time of diagnosis, years, range (mean ±SD) | 17-50 (27.9 ±9.2) | 15-55 (31.4±8.9) | 15-55 (30.4 ±9.0) |
| Age at NTZ initiation, years, range (mean ±SD) | 21-63 (34.5±11.2) | 20-56 (36.6±9.6) | 20-63 (36.0 ±10.1) |
| Time from diagnosis at NTZ initiation, years, range (mean ±SD) | 0-21 (6.2±5.8) | 0-25 (5.3±5.6) | 0-25 (5.5 ±5.6) |
| EDSS at the time of diagnosis, range (mean ±SD) | 1.0-6.0 (2.6±1.6) | 0-5.0 (2.0±1.3) | 0-6.0 (2.2 ±1.4) |
| EDSS at NTZ initiation, range (mean ±SD) | 1.0-7.5 (4.0±1.8) | 0-7.0 (3.4±1.8) | 0-7.5 (3.6 ±1.8) |
| Duration of NTZ treatment | | | |
| < 12 months, n (%) | 4 (16.7 %) | 9 (13.8 %) | 13 (14.6 %) |
| 12-36 months, n (%) | 15 (62.5 %) | 38 (58.5%) | 53 (59.6 %) |
| > 36 months, n (%) | 5 (20.8 %) | 18 (27.7 %) | 23 (25.8 %) |
| Primary reason for the cessation of NTZ treatment, | | | |
| Risk of PML considered too high*, n (%) | 11 (45.8 %) | 50 (76.9 %) | 61 (68.5 %) |
| Inefficacy of treatment, n (%) | 7 (29.2%) | 9 (13.8%) | 16 (18.0 %) |
| Pregnancy plans or pregnancy, n (%) | 4 (16.7%) | 3 (4.6%) | 7 (7.9 %) |
| Adverse events, n (%) | 1 (4.2 %) | 2 (3.1 %) | 3 (3.4 %) |
| Difficulties with peripheral venous cannulation, n (%) | 1 (4.2%) | 0 (0 %) | 1 (1.1 %) |
| Patient's own wish to discontinue treatment, n (%) | 0 (0 %) | 1 (1.5 %) | 1 (1.1 %) |

Table 2. The distribution of disease-modifying drugs used immediately prior to the initiation of natalizumab.

| | n | % |
|---|---|---|
| Glatiramer acetate | 35 | 39.3 |
| Subcutaneous interferons | 28 | 31.5 |
| Mitoxantrone | 8 | 9.0 |
| Azathioprine | 4 | 4.5 |
| Fingolimod | 1 | 1.1 |
| No disease-modifying drugs before natalizumab | 13 | 14.6 |

Table 3. The distribution of patients according to use of subsequent disease-modifying drugs (DMDs) and length of washout. The proportions of patients with corticosteroid-treated relapses at 6 and 12 months are presented within each group.

| | No. of patients in group | Corticosteroid-treated relapse at 0-6 months, n (%) | Corticosteroid-treated relapse at 0-12 months, n (%) |
|---|---|---|---|
| No subsequent DMDs | 20 | 4 (20.0 %) | 8 (40.0 %) |
| DMD initiated after 0-3 months of washout | 13 | 1 (7.7 %) | 4 (30.8 %) |
| DMD initiated after >3 months of washout | 56 | 13 (23.2 %) | 15 (26.8 %) |
| All patients | 89 | 18 (20.2 %) | 27 (30.3 %) |

Table 4. The results of the statistical analysis. Hazard rations (HR) and 95 % confidential intervals (95 % CI) are displayed for the statistically significant findings. For clarity, results with p>0.05 have been removed. NTZ = natalizumab, EDSS = Expanded Disability Status Scale, DMD = disease-modifying drug. *p<0.05, **p<0.01, ***p<0.001.

| | 6 months<br>HR (95 % CI) | 12 months<br>HR (95 % CI) |
|---|---|---|
| Univariate analysis | | |
| No. of relapses during the year before initiation of NTZ | 1.71 (1.29-2.27)*** | 1.66 (1.29-2.14)*** |
| EDSS 5.5 or higher at the initiation of NTZ | 2.84 (1.05-7.69)* | - |
| EDSS 5.5 or higher at the discontinuation of NTZ | 3.64 (1.38-9.57)** | 2.94 (1.28-6.72)* |
| Gender | - | - |
| Age at the initiation of NTZ | - | - |
| Time from diagnosis | - | - |
| Number of NTZ infusions | - | - |
| Multifocal onset symptoms | - | - |
| Multivariate analysis | | |
| No. of relapses during the year before initiation of NTZ | 1.65 (1.26-2.15)*** | 1.54 (1.21-1.96)*** |
| EDSS 5.5 or higher at the initiation of NTZ | 3.7 (1.23-11.15)* | - |
| EDSS 5.5 or higher at the discontinuation of NTZ | - | 2.63 (1.12-6.20)* |
| The effect of subsequent DMDs<br>(univariate Cox regression with patient as a random effect) | | |
| First-line DMD 0-3 months of washout | - | - |
| First-line DMD >3 months of washout | 7.69 (1.40-42.19)* | - |
| Second-line DMD 0-3 months of washout | - | - |
| Second-line DMD >3 months of washout | 3.94 (1.11-14.08)* | - |

Table 5. Descriptive data of all eight patients who had experienced rebound. DMD = disease-modifying drug, NTZ = natalizumab, EDSS = Expanded Disability Status Scale

| Patient | No. of previous DMDs | No. of NTZ infusions before discontinuation | No. of relapses during the year before NTZ | No. of relapses during the year after NTZ | EDSS at initiation of NTZ | EDSS at discontinuation of NTZ |
|---|---|---|---|---|---|---|
| 1 | 2 | 6 | 2 | 3 | 4.0 | 4.0 |
| 2 | 2 | 33 | 2 | 3 | 2.0 | 1.5 |
| 3 | 3 | 38 | 5 | 7 | 2.0 | 2.0 |
| 4 | 2 | 11 | 2 | 3 | 6.0 | 6.5 |
| 5 | 2 | 12 | 2 | 3 | 4.0 | 4.0 |
| 6 | 3 | 41 | 0 | 2 | 3.0 | 4.0 |
| 7 | 2 | 12 | 1 | 3 | 6.5 | 7.0 |
| 8 | 2 | 6 | 2 | 3 | 6.0 | 6.5 |